Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 208 (2021) 1–3

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Vaccine-induced immune thrombotic thrombocytopenia after the BNT162b2 mRNA Covid-19 vaccine: A case study

Vaccination is an effective strategy to reduce the burden of the coronavirus disease 2019 (COVID-19) pandemic. A number of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been approved and proven highly effective, without a counterbalancing safety signal in randomized trials [1–4].

In February 2021, a prothrombotic syndrome was described in patients who had received the ChAdox1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India), an adenoviral vector-based vaccine [5]. Subsequently, similar findings were reported in a small number of patients who had received the Ad26.COV2.S vaccine (Janssen; Johnson & Johnson), another adenoviral vector-based vaccine [6]. This syndrome has been called vaccine-induced immune thrombotic thrombocytopenia (VITT) [7], and consists of thrombotic complications, such as cerebral vein thrombosis, associated with thrombocytopenia. It is thought that antibodies against platelet factor 4 (PF4; CXCL4) play a pivotal role in the pathophysiology of VITT [8]. These antibodies potently activate platelets via platelet FcγIIa receptors (receptors on the platelet surface that bind the Fc portion of IgG), with platelet activation greatly enhanced by PF4.

We present a case report of an individual who developed VITT 5 days after administration of the BNT162b2 Covid-19 vaccine (Pfizer-BioNTech), a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein [1].

A 78-year-old man presented to the emergency room on May 17, 2021 with a 3-day history of shortness of breath and right lower extremity swelling. The patient had received the first dose of the BNT162b2 Covid-19 vaccine 25 days prior to admission, and the second dose 5 days prior to admission. Physical examination was notable for a heart rate of 116 beats per minute, blood pressure of 163/75 mmHg, oxygen saturation of 94% while breathing ambient air, normal cardiopulmonary examination, and right lower extremity swelling.

He had a history of prostate cancer and underwent curative prostatectomy in 2009, with no sequelae in subsequent follow-up visits. His past medical history was otherwise unrevealing. The patient was taking simvastatin on a regular basis, and he had not received any heparin products for 10 years.

Initial laboratory tests were notable for thrombocytopenia (platelet count, 117,000 per cubic millimeter [reference range, 140,000 to 440,000]), lower from his baseline value of 215,000 per cubic millimeter 4 months prior, and elevation in the D-dimer levels (>35,000 ng/mL [reference value, 208 to 500]) (Table 1). SARS-CoV-2 RNA was not detected on reverse-transcriptase-polymerase-chain-reaction assay of a sample obtained with a nasopharyngeal swab. Computed tomographic (CT) angiography of the chest demonstrated pulmonary embolism (PE) in the segmental and subsegmental arteries of both lungs, without right ventricle dilatation. Thrombosis of the right great saphenous vein and right distal (gastrocnemius) deep vein thrombosis (DVT) were diagnosed by compression ultrasonography.

An enzyme immunoassay (EIA) test (AESKULISA HiT II, AESKU.GROUP) was ordered and was positive (1.846 optical density [OD] units [upper limit of normal range, ≤0.396]). The result of a second EIA test (Asserachrom HPIA IgG, Stago) was 2.07 times higher than the cut-off OD (0.28) calculated according to manufacturer's protocol. Platelet reactivity was assessed using a heparin-induced platelet aggregation test (HIPA) (TA-8V aggregometer, Stago). Platelet-rich plasma (PRP) was prepared according to the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee ISTH SSC recommendations provided for platelet testing [9]. The HIPA assay reported a platelet aggregation of 39% with a concentration of 1 IU/mL unfractionated heparin.

The patient was started on anticoagulation with apixaban 10 mg twice daily and the clinical symptoms rapidly resolved. He was discharged on hospital day 4 with a diagnosis of VITT, and reduced the dose of apixaban to 5 mg twice daily after the first week of therapy.

Recent reports concluded that vaccination with adenovirus vector-based DNA vaccines may lead to rare thrombotic thrombocytopenia [5,7]. Some investigators have suggested that VITT is not a consequence of antibodies directed against the SARS-CoV-2 spike protein (produced by all vaccines) cross-reacting with PF4, but it is the adenovirus vector-based vaccines that are at risk of inducing VITT through adenovirus and/or other PF4-DNA interactions [8]. Though SARS-CoV-2 vaccination itself might induce the development of high titer PF-4 antibodies [10], this case meets the Brighton Collaboration case definition of VITT, with thrombocytopenia and thrombosis without prior heparin exposure [11]. Of note, it also fulfills the additional diagnostic criteria outlined in guidance by the International Society on Thrombosis and Haemostasis, including an elevated D-dimer level [12]. There was no clinical evidence consistent with other causes of thrombosis and thrombocytopenia (e.g., recent orthopedic surgery, SARS-CoV-2 infection, other infections, immune thrombocytopenia, or thrombotic thrombocytopenic purpura). The patient had normal platelet counts in prior encounters and was not using therapies that could potentially influence the platelet count. Although we cannot rule out atypical HIT, we believe the evidence might support a diagnosis of VITT in this case. This syndrome has been described after administration of the COVID vaccine 4 to 42 days prior to symptom onset, and VITT in this patient might be related to the administration of the first dose rather than the second one. As in a recent report

https://doi.org/10.1016/j.thromres.2021.10.002
Received 29 July 2021; Received in revised form 30 September 2021; Accepted 3 October 2021
Available online 9 October 2021

Table 1
Laboratory data.

Variable	Reference range	January 15, 2021	On presentation, May 17, 2021	May 18, 2021	May 20, 2021	May 31, 2021
Hemoglobin (g/dL)	13.3–16.7	15.8	14.0	14.0	15.3	NA
Hematocrit (%)	39–50	48.5	40.3	41.5	48.4	NA
White-cell count (per mm^3)	3.7–9.5	7.61	8.44	7.69	7.98	NA
Platelet count (per mm^3)	140–440	215	117	127	194	NA
Creatinine (mg/dL)	0.6–1.3	0.82	0.82	0.81	0.84	0.78
Aspartate aminotransferase (U/L)	4–50	NA	23	24	32	25
Alanine aminotransferase (U/L)	5–40	NA	14	14	22	19
C-reactive protein (mg/dL)	0.0–5.0	NA	80.5	NA	NA	NA
Prothrombin time (*sec*)	9–15	NA	11.7	11.1	12.4	11.7
International normalized ratio	0.86–1.13	NA	1.02	1.00	1.05	1.00
Partial-thromboplastin time (sec)	24.6–40	NA	29.0	28.7	30.8	30.8
Fibrinogen	150–600	NA	554.7	580.7	740	656.1
D-dimer (ng/mL)	208–500	NA	>35,000	NA	3889	1681
Factor V Leiden	–	NA	NA	NA	NA	Negative
Prothrombin gene mutation	–	NA	NA	NA	NA	Negative
Anti-β-2-glycoprotein-1 (U/mL)						
IgM	0–7	NA	NA	NA	NA	0.36
IgG	0–7	NA	NA	NA	NA	0.75
Anti-cardiolipin (U/L)						
IgM	0–10	NA	NA	NA	NA	0.05
IgG	0–10	NA	NA	NA	NA	0.68

NA denotes not assessed.

[13], the current case suggests that the rare occurrence of VITT could be also related to mRNA vaccines, raising the possibility of a common link between these vaccines. Future studies should elucidate whether platelet-activating antibodies are induced by the inflammatory stimulus of vaccination, or what component or components of the vaccine elicit a new (or recall) response to an unrelated host protein, PF4.

Although a remarkably high percentage of the patients with VITT had thromboses at unusual sites (cerebral venous sinus thromboses or thrombosis in the splanchnic veins), PE and DVT have also been described [8]. The pathophysiologic explanation for these unusual sites of thrombosis is unknown, and it might reflect a propensity to study patients with severe thrombosis occurring in unusual locations. In addition, previous cases have reported lower platelet counts (20,000 to 30,000 per cubic millimeter) [14]. It is possible that patients with typical thromboembolic events and mild thrombocytopenia (or normal platelet count) might be in an early stage of VITT.

There is very little information available related to the management of VITT. Although VITT occurs in the absence of heparin exposure, there is consensus to avoid heparin-based anticoagulants. Since the clinical and analytical course showed very rapid improvement, our patient did not receive intravenous immunoglobulin as recommended [12]. Additional research is needed to determine whether early recognition might decrease the high mortality rate associated with this process, and what treatment options may benefit patients with both typical and atypical presentations.

The patient is on anticoagulation and remains asymptomatic at the time of this report (last contact, August 30th, 2021).

In conclusion, VITT may be a rare occurrence after mRNA vaccination against SARS-CoV-2. Clinician and patients should be vigilant about this rare occurrence.

Funding

None.

Disclosures

None.

Declaration of competing interest

None.

References

[1] F.P. Polack, S.J. Thomas, N. Kitchin, et al., Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine, N. Engl. J. Med. 383 (2020) 2603–2615.
[2] L.R. Baden, H.M. El Sahly, B. Essink, et al., Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, N. Engl. J. Med. 384 (2021) 403–416.
[3] M. Voysey, S.A. Costa Clemens, S.A. Madhi, et al., Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials, Lancet 397 (2021) 881–891.
[4] J. Sadoff, G. Gray, A. Vandebosch, et al., Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19, N. Engl. J. Med. 384 (2021) 2187–2201.
[5] N.H. Schultz, I.H. Sorvoll, A.E. Michelsen, et al., Thrombosis and thrombocytopenia after ChAdOx1 nCoV vaccination, N. Engl. J. Med. 384 (2021) 2124–2130.
[6] K.L. Muir, A. Kallam, S.A. Koepsell, K. Gundabolu, Thrombotic thrombocytopenia after AD26.COV2.S vaccination, N. Engl. J. Med. 384 (2021) 1964–1965.
[7] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, N. Engl. J. Med. 384 (2021) 2092–2101.
[8] G. Uzun, K. Althaus, T. Bakchoul, No correlation between anti-PF4 and anti–SARS-CoV-2 antibodies after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. (2021), NEJMc2111305, https://doi.org/10.1056/NEJMc2111305.
[9] I. Nazy, U.J. Sachs, D.M. Arnold, et al., Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from ISTH SSC Subcommittee on platelet immunology, J. Thromb. Haemost. 19 (2021) 1585–1588.
[10] T. Thiele, L. Ulm, S. Holtfreter, et al., Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2, Blood 138 (2021) 299–303.

[11] Brighton Collaboration, Interim case definition of thrombosis with thrombocytopenia syndrome (TTS), Accessed at, https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition. on 31 August 2021.
[12] International Society on Thrombosis and Haemostasis, ISTH interim guidance for the diagnosis and treatment on vaccine-induced immune thrombotic thrombocytopenia, Accessed at, https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH_VITT_Guidance_2.pdf. on 31 August 2021.
[13] S. Sangli, A. Virani, N. Cheronis, et al., Thrombosis with thrombocytopenia after the messenger RNA–1273 vaccine, Ann. Intern. Med. (2021) L21–L0244, https://doi.org/10.7326/L21-0244.
[14] D.B. Cines, J.B. Bussel, SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, N. Engl. J. Med. 384 (2021) 2254–2256.

Carmen Rodríguez[a,1], Alberto Pérez-Nieva[b,1], Luis Máiz[a], María del Mar Meijón[c], Pilar Llamas[d], Manuel Monreal[e,f], Behnood Bikdeli[g,h,i], David Jiménez[a,f,*]

[a] *Respiratory Department, Ramón y Cajal Hospital, IRYCIS, Madrid, Spain*
[b] *Department of Internal Medicine, Ramón y Cajal Hospital, IRYCIS, Madrid, Spain*
[c] *Hematology Department, Ramón y Cajal Hospital, IRYCIS, Madrid, Spain*
[d] *Hematology Department, Fundación Jiménez Díaz, Madrid, Spain*
[e] *Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[f] *CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain*
[g] *Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[h] *Center for Outcomes Research and Evaluation (CORE), Yale School of Medicine, New Haven, CT, USA*
[i] *Clinical Trials Center, Cardiovascular Research Foundation, New York, NY, USA*

[*] Corresponding author at: Respiratory Department, Ramón y Cajal Hospital, IRYCIS, Alcalá University, 28034 Madrid, Spain.

[1] Both authors contributed equally to the manuscript.